Cytokine balance peculiarities in pregnant women operated for the thyroid gland during pregnancy

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The peculiarities of cytokine metabolism in women operated on the thyroid gland during pregnancy before and after surgery are represented in this publication. It was stated that the cytokine dysbalance is more meaningful in pregnant with diffuse toxic goiter. The surgery with the consequent hormone replacement therapy had the positive influence on the thyroid hormones metabolism. The hormone replacement therapy by micronized progesterone in women with signs of threatened abortion led to the improvement of pregnancy cytokine paradigm.
Key words: *thyroid gland, cytokine, pregnancy, thyroid surgery.*

During the last twenty years it has been observed higher frequency of surgical procedures on the thyroid gland during pregnancy when cancer is detected or there are recommendations for open treatment when conservative treatment of diffuse toxic goiter is inefficient [8]. Therefore, there arising a number of questions related to prenatal care for such women, including prevention of threatened miscarriage. It is proved that physiologic gestation period is associated with formation of immunological tolerance to fetus alloantigen. During this period it is activated a natural mechanism of inhibiting response for antigens of a foreign organism, that prevents reaction of fetus rejection. Within normal gestation course, suppression of a specific element of the immune system is compensated by activation of the nonspecific immunity system. Disorders in adequate change of the cytokine balance can be a cause of feto-maternal disease. According to the modern concepts, progress of inadequate immune reactions during gestation is one of the main reasons of pregnancy complications, the most dangerous results in pregnancy loss. In the first trimester the domination of Th1-cytokine activity results in miscarriage; during subsequent terms it is connected with gestosis development as many authors suppose. Availability of adverse background in a form of somatic pathology, influence of negative psychosocial characteristics can cause failure of adaptation mechanisms and generation of a symptom complex of threatening miscarriage or premature delivery threat [4, 7].

Today much attention is paid to prevention of habitual miscarriage and selection of a correct approach to prevent threatening miscarriage. In case when women having disorders of thyroid function the threatening miscarriage is the result of more than one reason that affect simultaneously or sequentially during the gestation course [2, 3, 6].

In initiation of threatening miscarriage as well as spontaneous miscarriage the main role is played by immune mechanisms that activate cell-mediated responses and biochemical reactions starting up a cascade of pathophysiological processes and resulting in fetus rejection. However, in case of normal gestation course trophoblast structures generate a whole group of immunomodulatory effects [6, 7].

Special attention should be given to data on influence of a higher level of autoimmune antibodies on hormones and tissues that provide considerable importance for normal pregnancy progress (on chorionic gonadotropin, estradiol, progesterone, growth hormones, thyroid hormones, ovary tissues, cell nucleus structures, DNA molecules) and their connection with uncertain reproductive losses [1, 3, 5].

Therefore, the goal of this research has become **studying of cytokine balance peculiarities of women operated on the thyroid gland during pregnancy**.

MATERIALS AND METHODS

In this research it is carried out an analysis of changes in regulatory mechanisms in pregnant women who underwent surgical treatment on thyroid gland pathology during pregnancy. There were determined levels of interleukins IL-1, IL-2, IL-6, tumor necrosis factor-α (TNF-α) by means of test kits produced by Vektor-Best, Saint Petersburg, according to a specification of the producer. The analysis included examination of 36 pregnant women having thyroid cancer (I group) and 30 pregnant women having diffuse toxic goiter (II group). Cortisol level was measured by an immune-enzyme method using a relevant set for IFA. The first group (28 women) includes pregnant women having thyroid cancer and high cortisol level, the second group (26 women) includes pregnant women having diffuse toxic goiter and high cortisol level. 30 pregnant women without thyroid gland pathology made a control group.

RESULTS AND DISCUSSION

Subject to provided certain indications in II trimester of pregnancy on surgical procedures on the thyroid gland caused determination of cytokine levels at this period.

Levels of selected for the research cytokines before surgical treatment are set out in table 1.

In the II trimester of pregnancy levels of IL-1 were higher for follicular and papillary forms of thyroid cancer than in the control group, but virtually they did not differ and made 27,5 and 29,4 pg/ml respectively.

It is apparently that IL-1 potentiates processes of synthesis and secretion of steroid hormones levels which effect the gestation course, and in particular, promote increase in secretion of progestogen and estrogens by placenta cells.

It was established significant increase of IL-1 and IL-6 secretion in case of women having diffuse toxic goiter (II group) as compared to pregnant women of the first and control groups. Subject to an autoimmune process a level of proinflammatory cytokines increases by more than 4 times.

Table 1

Interleukin levels in pregnant women in the second trimester before surgical treatment, pg/ml

Group of pregnant women	IL-1	IL-6	TNF-α
I	28,0±2,4*	37,3±4,3*	69,5±5,9*
II	35,0±3,7*	83,2±13,6*	50,0±10,4*
Control group	10,3±0,73	22,8±6,1	15,21±8,52

Notes:* – difference in levels is reliable in comparison to the control group ($p<0,05$).

Table 2

Interleukin levels in examined women in the second trimester after surgical treatment, pg/ml

Group of pregnant women	IL-1	IL-6	TNF-α
I	19,2±0,94*	30,3±3,1*	54,57±17,21*
II	25,8±0,97*	43,2±10,6*	35,61±11,56*
Control group	10,3±0,73	22,8±6,1	15,21±8,52

*Notes:** – difference in levels is reliable in comparison to the control group ($p<0,05$).

In the second group levels of TNF-α are appeared to be three-fold higher than in the control group, and in the first group this index exceeded indices of the control group by over four-fold ($p<0,001$).

Increase of TNF-α level in blood attends to activation of systemic nonspecific resistance of the organism against progress of a neoplastic process. It is found that TNF is the only cytokine that has direct cytotoxic effect on neoplastic cells. On the one hand, the cytotoxic effect of TNF-α can be realized by a membrane monomer of TNF-α receptor upon contacts of an immune competent cell with a target cell, and on the other hand, TNF-α trimer connected with transport molecules, can be transported with blood flow to effector cells. TNF-α trimer binds with TNF-α receptors on neoplastic cells and denaturates them. Despite the fact that the TNF receptor is available in all cells, only mutant cells bind with TNF-α and decay [5, 6].

During physiological gestation course TNF-α is determined in the uterus, decidual cells, and trophoblast. It is considered that during early pregnancy it participates in immune surveillance and facilitates an inflammatory process around oocyte development area, later it is involved in regulation of tissue differentiation, blood formation. At the end of pregnancy a monokine activates biosynthesis of prostaglandins and facilitates onset of delivery. It is possible that in case of the feto-maternal disease increase in the TNF-α level causes substantial increase of a number of trophoblast proapoptotic cells, and it can be one of factors that cause threatening miscarriage. In addition, some researches proved that excessive generation of TNF-α, IL-1 can result in development of depression [2, 4].

Data on levels of the studied cytokines upon surgical treatment are set out in table 2.

Upon surgical treatment the pregnant women received replacement hormonal therapy by levothyroxine. As shown in the Table 2 the studied cytokines decreased but they were far from indices for the control group levels.

Analyzing data related to the fact that the most examined women had symptoms and ultrasound signs of threatening miscarriage, and analyzing levels of interleukin in tables 1 and 2 it is possible to think about reduction in progesterone effect, or affection of the receptors to progesterone that causes decrease in synthesis of PIBF (progesterone induced blocking factor).

Under a low level of endogenous progesterone or affection of the receptors to progesterone it is reduced synthesis of the blocking factor induced by progesterone (PIBF). Effecting natural killers (NK-cells, CD16+cells) PIBF has protective influence on pregnancy, reroutes response of the maternal organism to the fetus to less active cells: large granular lymphocytes that bear markers CD56+ CD16+. Subject to availability of such cells the immune response of the mother is implemented through T-helpers of II type (ThII) that generate regulatory cytokines IL-3, IL-4, IL-10, IL-13. Under the low level of progesterone or affection of progesterone receptors PIBF amount is respectively decreasing. Under these conditions the immune response of the mother to trophoblast is shifting to lymphoquin: activated killers (LAK that bear markers CD56+ CD16+) and to more active response through T-helpers of I type (ThI) with generation of anti-inflammatory cytokines (IL-1, IL-6, TNF-α).

To eliminate the symptoms of threatening pregnancy these women are recommended to replace hormones by micronized progesterone by 200 mg twice per day.

During the research it was also established that among women of both groups where it is detected the higher level of cortisol it was observed substantial increase of IL-6 secretion as compared to women without the higher level of cortisol and the control group. IL-6 secretion is stimulated by TNF-α and IL-1. In its turn IL-6 suppresses further generation of TNF-α and IL-1. Some effects caused by IL-6 are similar to those observed in effects of IL-1 and TNF. However, the main effect of IL-6 is connected with its involvement as a cofactor in differentiation of B-lymphocytes, their maturation and transformation into plasmatic cells that secrete immunoglobulin. Moreover, ILЛ-6 facilitates expression of IL-2 receptor on activated immunocytes, and induces secretion of IL-2 by means of T-cells. This cytokine stimulates proliferation of T-lymphocytes and hemogenesis reaction [1, 5].

By variety of cell generation sources and targets of biological effect IL-6 is one of the most active cytokines that participate in implementation of the immune response and the inflammatory response.

As a result of animal model research it is found that stress increases level of endogenous IL-6. These data attends to a fact that during stress secretion of IL-6 takes place (probably mediated by adrenoreceptors), and that IL-6 participates in development of stress response. IL-6 also has a significant stimulating effect on stress response system [6].

The high level of IL-6 and increased cortisol level attend to a high stress level of such women. Hypersecretion of IL-6 and the increased cortisol level of women with signs of threatening miscarriage testifies to adverse effect of stress on the gestation course. Under stress conditions thyronine along with decrease of adrenoreactivity results in antistress effect, and their deficiency

Table 3

Interleukin levels of women from the study groups after hormone replacement therapy and psychocorrection, pg/ml

Group of pregnant women	Interleukin indices depending on treatment period (before, after)			
	IL-2		IL-6	
	DT	DT + PF	DT	DT + PF
1	33,6±5,61*	47,2±3,51*	35,6±4,7*	23,7±3,2*
2	31,6±5,64*	50,2±4,12*	42,2±4,1*	24,1±3,8*
Control group	57,6±9,42		22,8±6,1	

*Notes:** – difference in levels is reliable in comparison to the control group ($p<0,05$).

facilitate increase in stress susceptibility. Inadequate function of the TG before surgical treatment is able to impair not only general metabolic processes in the organism, but also to decrease resistance to stress. It is the reason why women from groups I and II were recommended to have psychological follow-up (PF) of gestation (art therapy, discussions and sessions with a perinatal psychologist), in addition to medicine treatment (DT).

In Table 3 shown data on immune status of women upon relevant treatment.

According to the data in Table 4 the indices of pregnancy paradigm (Th1/Th2) reached the level of the control group in both study groups.

Analysis of the conducted researches showed that a criterion of threatening miscarriage and early delivery threat can be increased in the level of proinflammatory cytokines IL-1, IL-6 TNFα. In the postoperative period prescription of micronized progesterone therapy against threatening miscarriage to women in the study groups optimizes cytokine balance with recovery of pregnancy paradigm.

CONCLUSIONS

1. Women operated on the thyroid gland during pregnancy have cytokine imbalance that attends to substantial changes of the immune status in this group of women.

2. It should be noted that in the group of pregnant women having diffuse toxic goiter it is detected more serious disorders of cytokine metabolism than in group with thyroid cancer that is explained due to a trigger mechanism: autoimmune process in the thyroid gland.

3. In both groups singled out women with the increased cortisol level, actually in these women with higher frequency of ultrasound and laboratory signs of threatening miscarriage, as well as complication symptoms.

4. In case of women operated on the thyroid gland during pregnancy medical and psychological follow-up including micronized progesterone, art therapy, discussions and sessions with a perinatal psychologist are scientifically proved, that results in advance of cytokine balance indices to the normal paradigm during pregnancy.

Сведении об авторах

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Особливості балансу цитокинів у вагітних, оперованих на щитоподібній залозі під час вагітності

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Особливості метаболізму цитокінів у жінок, оперованих на щитоподібній залозі під час вагітності до і після операції, наведені у статті. Було виявлено, що дисбаланс цитокінів є більш вираженим у вагітних з дифузним токсичними зобом. Оперативне втручання з подальшим призначенням замісної гормональної терапії мало позитивний вплив на метаболізм гормонів щитоподібної залози. Замісна гормональна терапія мікронізованим прогестероном у жінок з ознаками загрози переривання вагітності призвела до поліпшення парадигми вагітності за рівнем цитокінів.

Ключові слова: *щитоподібна залоза, цитокін, вагітність, хірургія.*

Особенности баланса цитокинов у беременных, оперированных на щитовидной железе во время беременности

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Особенности метаболизма цитокинов у женщин, оперированных на щитовидной железе во время беременности до и после операции, приведены в статье. Установлено, что дисбаланс цитокинов является более выраженным у беременных с диффузным токсическим зобом. Операция и последующее назначение заместительной гормональной терапии имели положительное влияние на метаболизм гормонов щитовидной железы. Заместительная гормональная терапия микронизированным прогестероном у женщин с признаками угрозы прерывания беременности привела к улучшению парадигмы беременности по уровню цитокинов.

Ключевые слова: *щитовидная железа, цитокин, беременность, хирургия.*

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